NATIONAL MARROW DONOR PROGRAM®

Entrusted to operate the C.W. Bill Young Cell Transplantation Program,
including Be The Match Registry®

July 26, 2012

CDR Sheri Parker
Office of Naval Research (ONR 342)
875 N. Randolph St.
Arlington, VA 22203-1995

Subject: **Quarterly Performance/Technical Report of the National Marrow Donor Program®**

Reference: Grant Award #N00014-11-1-0339 between the Office of Naval Research and the National Marrow Donor Program

Dear Cdr. Parker:

Enclosed is subject document which provides the performance activity for each statement of work task item of the above reference for the period of April 1, 2012 to June 30, 2012.

Should you have any questions as to the scientific content of the tasks and the performance activity of this progress report, you may contact our Chief Medical Officer – Dennis L Confer, MD directly at 612-362-3425.

With this submittal of the quarterly progress report, the National Marrow Donor Program has satisfied the reporting requirements of the above reference for quarterly documentation. Other such quarterly documentation has been previously submitted under separate cover.

Please direct any questions pertaining to the cooperative agreement to my attention at 612-362-3403 or at cabler@nmdp.org.

Sincerely,

Carla Abler-Erickson

Carla Abler-Erickson, MA
Contracts Manager

Enclosure: Quarterly Report with SF298

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
26-07-2012	Quarterly	Apr – Jun 2012

4. TITLE AND SUBTITLE
Development of Medical Technology for Contingency Response to Marrow Toxic Agents - Quarterly Performance/Technical Report for April 01, 2012 to June 30, 2012 Period 5

5a. CONTRACT NUMBER
N/A

5b. GRANT NUMBER
N00014-11-1-0339

5c. PROGRAM ELEMENT NUMBER
N/A

6. AUTHOR(S)
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5d. PROJECT NUMBER
N/A

5e. TASK NUMBER
Project 1, 2, 3, 4

5f. WORK UNIT NUMBER
N/A

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
National Marrow Donor Program
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8. PERFORMING ORGANIZATION REPORT NUMBER
N/A

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Office of Naval Research
875 N. Randolph St.
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10. SPONSOR/MONITOR'S ACRONYM(S)
ONR

11. SPONSORING/MONITORING AGENCY REPORT NUMBER
N/A

12. DISTRIBUTION AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited

13. SUPPLEMENTARY NOTES
N/A

14. ABSTRACT

1. Contingency Prepardness: Collect information from transplant centers, build awareness of the Transplant Center Contingency Planning Committee and educate the transplant community about the critical importance of establishing a nationwide contingency response plan.

2. Rapid Identification of Matched Donors : Increase operational efficiencies that accelerate the search process and increase patient access are key to preparedness in a contingency event.

3. Immunogenetic Studies: Increase understanding of the immunologic factors important in HSC transplantation.

4. Clinical Research in Transplantation**:** Create a platform that facilitates multicenter collaboration and data management.

15. SUBJECT TERMS
Research in HLA Typing, Hematopoietic Stem Cell Transplantation and Clinical Studies to Improve Outcomes

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE	Same as Report	16	Dennis L. Confer, MD – Chief Medical Office
U	U	U			19b. TELEPONE NUMBER (*Include area code)* 612.362.3425

Grant Award N00014-11-1-0339

DEVELOPMENT OF MEDICAL TECHNOLOGY FOR CONTINGENCY RESPONSE TO MARROW TOXIC AGENTS

QUARTERLY PERFORMANCE / TECHNICAL REPORT

FOR

APRIL 01, 2012 to JUNE 30, 2012

PERIOD 6

Office of Naval Research

And

The National Marrow Donor Program
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IIA. Contingency Preparedness – Objective 1: Recovery of casualties with significant myelosuppression following radiation or chemical exposure is optimal when care plans are designed and implemented by transplant physicians	
IIA.1 Task 1: Secure Interest of Transplant Physicians	**Period 6 Activity:** • No activity this period.
IIA.1 Task 2: GCSF in Radiation Exposure	**Period 6 Activity:** • No activity this period.
IIA.1 Task 3: Patient Assessment Guidelines and System Enhancements	**Period 6 Activity:** • No activity this period.
IIA 1 Task 4: National Data Collection Model – This task is closed.	
IIA. Contingency Preparedness – Objective 2: Coordination of the care of casualties who will require hematopoietic support will be essential in a contingency situation.	
IIA.2 Task 1: Contingency Response Network	**Period 6 Activity:** • Hired a contractor on a part time basis to assist with the performance of RITN hospital site assessments • Attended the Armed Forces Radiobiology Research Institute's (AFRRI) conference on advances in treating combined injuries resulting from a radiological disaster • Continued the development of a Full Scale Exercise to be held at Memorial Sloan Kettering Cancer Center in NYC on November 15th, 2012; the exercise initial planning conference was held in June and the follow-up conference will be held in August • The web based learning management system (LMS) implementation continues with vendor SumTotal o Pilot launch to employees in April 2012; pilot launch to NMDP Network, RITN and all NMDP staff in August 2012

IIA.2 Task 2: Sibling Typing Standard Operating Procedures	**Period 6 Activity:** • No activity this period.
IIA. Contingency Preparedness – Objective 3: NMDP's critical information technology infrastructure must remain operational during contingency situations that directly affect the Coordinating Center.	
IIA.3 Task 1: I.S. Disaster Recovery	**Period 6 Activity:** • No activity this period.
IIA.3 Task 2: Critical Facility and Staff Related Functions	**Period 6 Activity:** • No activity this period
IIB. Rapid Identification of Matched Donors – Objective 1: Increasing the resolution and quality of the HLA testing of volunteers on the registry will speed donor selection.	
IIB.1 Task 1: Increase Registry Diversity	**Period 6 Activity:** • In May 2012 one staff member traveled to Liverpool England to attend the IHIW/EFI meeting. Data was presented on the NMDP experience of retyping of rare alleles at the "Frequency of Rare Alleles Workshop" and a poster abstract was presented on the inaccuracy of DRB1*16:08 typed donors in the Be The Match Registry.
IIB.1 Task 2: Evaluate HLA-DRB1 High Res typing – This task is closed.	
IIB.1 Task 3: Evaluate HLA-C Typing of Donors – This task is closed	
IIB.1 Task 4: Evaluate Buccal Swabs	**Period 6 Activity:** • No activity this period.
IIB 1 Task 5: Enhancing HLA Data for Selected Donors – This task is closed.	

IIB 1 Task 6: Maintain a Quality Control Program	**Period 6 Activity:** During this quarter, 65 additional samples from the Research Repository were selected for incorporation into the NMDP QC program and sent for B-LCL cell culture/initiation/expansion. Six of the 110 samples sent in 2011 are still pending.
IIB. Rapid Identification of Matched Donors – Objective 2: Primary DNA typing data can be used within the registry to improve the quality and resolution of volunteer donor HLA assignments.	
IIB 2 Task 1: Collection of Primary Data	**Period 6 Activity:** • No activity this period.
IIB 2 Task 2: Validation of Logic of Primary Data – This task is closed.	
IIB 2 Task 3: Reinterpretation of Primary Data – This task is closed.	
IIB 2 Task 4: Genotype Lists & Matching Algorithm	**Period 6 Activity:** • Prototyped changes to Traxis GUI to display most likely alleles and show alternative genotypes in a tooltip. This is a pre-requisite to relaxing the need to encode HLA typing data into allele codes at the laboratory and allowing genotype lists to be reported and used for matching and on search reports. • Implemented search-server web service that returns genotype probabilities for a given donor and recipient for use in Silver Standard Traxis match result display. • GL string web services: We have developed web services that create, update, and retrieve HLA typing data in standardized formats without the need for allele codes and their inherent introduction of new ambiguities. ReSTful web services with content-aware negotiation are being developed employing a Java library that manages HLA typing data using standardized formats. These formats include the XML based Histoimmunogenetics Markup Language (HML), and a simple character deliminated string format able to encode HLA typing with its ambiguity (GLString). Resources are identified with a simple URI. The services access a database containing IMGT/HLA data which is updated quarterly, and objects such as alleles, lists of alleles, haplotypes, genotypes, and lists of genotypes. Public services include creating, deleting, updating, and retrieving these objects.

	Content negotiation allows retrieving these data in a variety of formats including GL String, HML, HTML, JSON, and QRCodes. The tools being developed here provide the HLA researcher and clinician a common resource for managing HLA data in a standardized way. We envision these tools to augment workflows, creating new instances of HLA typing objects when needed, and retrieval of those objects and their associated metadata when called upon. Researched current technologies available for sharing HLA information including NMDP's HML, Mitre's hData, HL7 Open Health Tools, and HL7 FHIR.
IIB. Rapid Identification of Matched Donors – Objective 3: Registry data on HLA allele and haplotype frequencies and on the nuances of HLA typing can be used to design computer algorithms to predict the best matched donor.	
IIB.3 Task 1: Phase I of EM Haplotype Logic	**Period 6 Activity:** • No activity this period.
IIB 3 Task 2: Enhancement of EM Algorithm	**Period 6 Activity:** • No activity this period.
IIB 3 Task 3: Optimal Registry Size Analysis	**Period 6 Activity:** • No activity this period.
IIB 3 Task 4: Target Under- Repre-sented Phenotypes	**Period 6 Activity:** • Presented new version of haplostats with BMDW and NEMO data at the IHIW/EFI meeting. Continue working on single sign on functionality for Bioinformatics applications.
IIB 3 Task 5: Bioinformatics Web Site – This task is closed.	
IIB 3 Task 6: Consultants to Improve Algorithm – This task is closed.	
IIB 3 Task 7: Population Genetics – This task is closed.	
IIB 3 Task 8: Haplotype Matching – This task is closed.	
IIB 3 Task 9: Global Haplotype/Benchmark – This task is closed.	

IIB. Rapid Identification of Matched Donors – Objective 4: Reducing the time and effort required to identify closely matched donors for patients in urgent need of HSC transplants will improve access to transplantation and patient survival in the context of a contingency response and routine patient care.	
IIB.4 Task 1: Expand Network Communications – This task is closed.	
IIB.4 Task 2: Central Contingency Management	**Period 6 Activity:** • Analysis to determine the 7/8 donor match rate continued for patient's of the 4 broad race groups; Caucasian, African, Hispanic and Asian-Pacific Islander. The HLA typing lab was selected and the contract was finalized. Donor search reviews are in progress and HLA typing has started. During this period HLA testing was performed on 725 loci for 650 donors. Donors are being tested in rounds of priority for cost efficiency. Donor search reviews and HLA testing will continue to complete the analysis.
IIB.4 Task 3: Benchmarking Analysis – This task is closed.	
IIB.4 Task 4: Expand Capabilities of Collection and Apheresis Centers – This task is closed.	
IIC. Immunogenetic Studies – Objective 1: HLA mismatches may differ in their impact on transplant outcome, therefore, it is important to identify and quantify the influence of specific HLA mismatches. In contingency situations it will not be possible to delay transplant until a perfectly matched donor can be found.	
IIC.1 Task 1: Donor Recipient Pair Project	**Period 6 Activity:** Donor Recipient Pair Project In 1994 a retrospective D/R Pair HLA typing project to characterize class I and class II alleles of donor/recipient paired samples from NMDP's Repository was initiated. The goals of this ongoing research project are to assay the impact of DNA-based HLA matching on unrelated donor transplant outcome, develop strategies for optimal HLA matching, evaluate the impact of matching at alternative HLA loci on transplant outcome and finally to promote the development of DNA-based high resolution HLA typing methodologies. Presence/absence typing of 14 KIR loci (2DL1-5, 2DS1-5, 3DL1-3 and 3DS1) has been included. • Auditing of HLA and KIR in SG27, SG 28 and SG 29 has continued. Discrepancy and no make resolution are ongoing. • KIR linkage analysis has been sent to all KIR typing labs. • SG30 contracts have gone out and data is being received.

	To date over 2500 pairs and 1180 additional donors have been typed for presence/absence of 14 KIR loci (2DL1-5, 2DS1-5, 3DL1-3 and 3DS1). Current HLA matching guidelines for unrelated HCT recommend avoidance of mismatches only within the Antigen Binding Domain (ABD). This recommendation is based on the hypothesis that amino acid differences outside the ABD are not immunogenic. The ABD allo-reactivity assessment project will give insight into the allowable percent tolerance of matching needed outside of the ABD. • Initial investigation of the class I non-ABD mismatches (A*02:01/02:09, B*44:02/44:27 and C*07:01/07:06) have been performed where both alleles have been seen in the same genotype. Specific queries of the Be The Match Registry allowed for selection of one hundred and forty potential donors to be typed at high resolution for the class I locus of interest. Data will be received in the next quarter.
IIC. Immunogenetic Studies – Objective 2: Even when patient and donor are HLA matched, GVHD occurs so other loci may play a role.	
IIC 2 Task 1: Analysis of non-HLA loci	**Period 6 Activity:** • The monthly HLA Save file with HLA and match grades for clinical outcomes research has been integrated into the new Immunobiology Integration DataBase (IIDB) after significant progress in quality assurance testing of this database.
IIC 2 Task 2: Related Pairs Research Repository – This task is closed.	
IIC 2 Task 3: CIBMTR Integration – This task is closed.	

IID. Clinical Research in Transplantation – Objective 1: Clinical research in transplantation improves transplant outcomes and supports preparedness for a contingency response.	
IID.1 Task 1: Observational Research, Clinical Trials and NIH Transplant Center	**Period 6 Activity:** **Cord Blood Research** • The Duke and St. Louis Cord Blood Bank (SLCBB) created and finalized plans for training and validating the assay methodologies to ensure the generation of consistent results at both testing sites for the study investigating biomarkers associated with cord blood engraftment. o Testing using this third laboratory, SLCBB, is under development to determine whether the poor reliability is due to center-specific or assay related issues. o The effort to procure and place a flow cytometer with the correct lasers to perform the assays within the specifications of the manufacturer is on-going. ▪ The lease agreement for SLCBB's study flow cytometer been signed. Placement and validation of the flow cytometer is expected to take place in the next quarter. • Development of the anti-HLA donor specific antibody study of recipients transplanted with cord blood units was initiated. o It was determined that the study cohort is too small to proceed with the study at this time. • Work continued on a study to assess CBU characteristics (viability, TNC, CFU and CD34) pre-freeze and post thaw. Segment evaluation prior to unit release was under consideration as a third evaluation point. Results of a survey to the cord blood banks were analyzed and the unit release testing data deemed too variable for meaningful analysis. The study will proceed with pre-freeze and post-thaw characteristics only. o The study was discussed during the Cord Blood Advisory Group in May. A task force for study development will be created during the next quarter.

	• Work was initiated and completed on an assessment of the impact of donor inherited paternal antigen (IPA) disparity on outcomes after unrelated cord blood transplantation (UCBT) for Acute Lymphoblastic Leukemia and Acute Myelogenous Leukemia. o Results were presented as a poster at the 2012 International Cord Blood Symposium in June. **Prospective Studies; RCI BMT** • The last site payments were distributed for subjects reaching the last follow up milestone related to the Adult Double Cord trial. • Database management continued related to the AdvantageEDC^{SM} system used for both the Double Cord and Revlimid trials.
IID.1 Task 2: Research with NMDP Donors – This task is closed.	
IID.1 Task 3: Expand Immuno-biology Research	**Period 6 Activity:** The CIBMTR IBWC met monthly during the quarter to discuss progress on ongoing research studies • The IBWC co-scientific director and biostatistician participated in the 16th International Histocompatibility and attended the IHIW/EFI joint meetings. • One abstract was presented: o Carolyn Hurley, et al., *Impact of unidirectional mismatches on the outcome of unrelated donor hematopoietic stem cell transplantation.* Oral presentation 2012 IHIW/EFI joint meetings. • Two manuscripts were submitted: o Vanderson Rocha et al., *Effect of HLA-matching recipient to donor non-inherited maternal antigens on outcomes after mismatched umbilical cord blood transplantation for hematologic malignancy.* Submitted to BBMT. o Lawrence Petz, et al., *The cure of HIV infections using cord blood transplantation.* Submitted BBMT. • Three manuscripts were published:

	o Stephen Spellman, et al., *A perspective on the selection of unrelated donors and cord blood units for transplantation.* Published in Blood. o Minoo Battiwalla, et al., *HLA DR15 antigen status does not impact graft-versus-host disease or survival in HLA-matched sibling transplantation for hematologic malignancies.* Published in BBMT. o Naynesh Kamani, et al., *Unrelated donor cord blood transplantation for children with severe sickle cell disease: Results of one cohort from the phase II study from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN).* Published in BBMT.

ACRONYM LIST

AABB	American Association of Blood Banks	HR	High Resolution
AFA	African American	HRSA	Health Resources and Services Administration
AGNIS	A Growable Network Information System	HSC	Hematopoietic Stem Cell
AIM	Ancestry Informative Markers	IBWC	Immunobiology Working Committee
AML	Acute Myelogenous Leukemia	IDM	Infectious Disease Markers
ABD	Antigen Binding Domain	IHWG	International Histocompatibility Working Group
API	Asian Pacific Islander	IMGT	ImMunoGeneTics
ARS	Acute Radiation Syndrome (also known as Acute Radiation Sickness)	IHIW	International Histocompatibility and Immunogenetics Workshop
ASBMT	American Society for Blood and Marrow Transplantation	IPR	Immunobiology Project Results
ASHI	American Society for Histocompatibility and Immunogenetics	ICRHER	International Consortium for Research on Health Effects of Radiation
B-LCLs	B-Lymphoblastoid Cell Lines	IND	Investigational New Drug
BARDA	Biomedical Advanced Research and Development Authority	IS	Information Services
BBMT	Biology of Blood and Marrow Transplant	IT	Information Technology
BCP	Business Continuity Plan	IRB	Institutional Review Board
BCPeX	Business Continuity Plan Exercise	JCAHO	Joint Commission on Accreditation of Healthcare Organizations
BMCC	Bone Marrow Coordinating Center	KIR	Killer Immunoglobulin-like Receptor
BMDW	Bone Marrow Donors Worldwide	MDACC	MD Anderson Cancer Center
BMT	Bone Marrow Transplantation	MDS	Myelodysplastic Syndrome
BMT CTN	Blood and Marrow Transplant - Clinical Trials Network	MHC	Major Histocompatibility Complex
BODI	Business Objects Data Integrator	MICA	MHC Class I-Like Molecule, Chain A
BRT	Basic Radiation Training	MICB	MHC Class I-Like Molecule, Chain B
C&A	Certification and Accreditation	MKE	Milwaukee
CAU	Caucasian	MRD	Minimal Residual Disease

CBMTG	Canadian Blood and Marrow Transplant Group	MSKCC	Memorial Sloan-Kettering Cancer Center
CBB	Cord Blood Bank	MSP	Minneapolis
CBC	Congressional Black Caucus	MUD	Matched Unrelated Donor
CBS	Canadian Blood Service	NAC	Nuclear Accident Committee
CBU	Cord Blood Unit	NCBM	National Conference of Black Mayors
CDA	Clinical Document Architecture	NCI	National Cancer Institute
CHTC	Certified Hematopoeitic Transplant Coordinator	NEMO	N-locus Expectation-Maximization using Oligonucleotide typing data
CIBMTR	Center for International Blood & Marrow Transplant Research	NHLBI	National Heart Lung and Blood Institute
CIT	CIBMTR Information Technology	NIH	National Institutes of Health
CLIA	Clinical Laboratory Improvement Amendment	NIMS	National Incident Management System
CME	Continuing Medical Education	NK	Natural Killer
CMF	Community Matching Funds	NLE	National Level Exercise
COG	Children's Oncology Group	NMDP	National Marrow Donor Program
CREG	Cross Reactive Groups	NRP	National Response Plan
CSS	Center Support Services	NST	Non-myeloablative Allogeneic Stem Cell Transplantation
CT	Confirmatory Testing	OCR/ICR	Optical Character Recognition/Intelligent Character Recognition
CTA	Clinical Trial Application	OIT	Office of Information Technology
CTMS	Clinical Trial Management System		
DC	Donor Center	OMB	Office of Management and Budget
DHHS-ASPR	Department of Health and Human Service – Assistant Secretary Preparedness and Response	ONR	Office of Naval Research
DIY	Do it yourself	P2P	Peer-to-Peer
DKMS	Deutsche Knochenmarkspenderdatei	PBMC	Peripheral Blood Mononuclear Cells
DMSO	Dimethylsulphoxide	PBSC	Peripheral Blood Stem Cell
DoD	Department of Defense	PCR	Polymerase Chain Reaction
DHHS-ASPR	Department of Health and Human Services –	PSA	Public Service Announcement

	Assistant Secretary for Preparedness and Response		
DNA	Deoxyribonucleic Acid	QC	Quality control
DR	Disaster Recovery	RCC	Renal Cell Carcinoma
D/R	Donor/Recipient	RCI BMT	Resource for Clinical Investigations in Blood and Marrow Transplantation
EBMT	European Group for Blood and Marrow Transplantation	REAC/TS	Radiation Emergency Assistance Center/Training Site
EDC	Electronic Data Capture	REMM	Radiation Emergency Medical Management
EFI	European Federation of Immunogenetics	RFP	Request for Proposal
EM	Expectation Maximization	RFQ	Request for Quotation
EMDIS	European Marrow Donor Information System	RG	Recruitment Group
ENS	Emergency Notification System	RITN	Radiation Injury Treatment Network
ERSI	Environment Remote Sensing Institute	SBT	Sequence Based Typing
FBI	Federal Bureau of Investigation	SCTOD	Stem Cell Therapeutics Outcome Database
FDA	Food and Drug Administration	SG	Sample Group
FDR	Fund Drive Request	SLW	STAR Link® Web
FHIR	Fast Healthcare Interoperability Resources	SNP	Single Nucleotide Polymorphism
FLOCK	Flow Cytometry Analysis Component	SSA	Search Strategy Advice
Fst	Fixation Index	SSO	Sequence Specific Oligonucleotides
GETS	Government Emergency Telecommunications Service	SSP	Sequence Specific Primers
GCSF	Granulocyte-Colony Stimulating Factor (also known as filgrastim)	SSOP	Sequence Specific Oligonucleotide Probes
GIS	Geographic Information System	STAR®	Search, Tracking and Registry
GvHD	Graft vs Host Disease	TC	Transplant Center
GTR	Genetic Testing Report	TED	Transplant Essential Data
HCS	HealthCare Standard	TNC	Total Nucleated Cell
HCT	Hematopoietic Cell Transplantation	TSA	Transportation Security Agency
HEPP	Hospital Emergency Preparedness Program	UI	User Interface

HHQ	Health History Questionnaire	UML	Unified Modeling Language
HHS	Health and Human Services	URD	Unrelated Donor
HIPAA	Health Insurance Portability and Accountability Act	VPN	Virtual Private Network
HIS	Hispanic	WGA	Whole Genome Amplification
HLA	Human Leukocyte Antigen	WMDA	World Marrow Donor Association
HML	Histoimmunogenetics Mark-up Language	WU	Work-up